

HISTORICAL SKETCH

AIDS, hepatitis and hemophilia in the 1980s: memoirs from an insider

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Introduction

On 7 June 2001 the *New England Journal of Medicine* highlighted the cases of *Pneumocystis carinii* pneumonia that 20 years before had heralded the onset of the AIDS outbreak with the publication of a Special Article, an Editorial and a Sounding Board article. I suspect that it was not by chance that in the same issue the Journal also published the preliminary results of the first clinical trial of gene transfer in patients with severe hemophilia A, together with an accompanying Editorial and a Medical Progress review article. Perhaps this choice of the journal of featuring the dramatic improvements brought about by DNA technology in the management of hemophilia was dictated by the special sympathy of the scientific community for a category of patients, i.e. persons with hemophilia and recipients of blood transfusion, who contracted AIDS as a consequence of their unavoidable need for life-saving treatments.

Before the 1980s and the ravages of AIDS, the 1970s had witnessed dramatic improvements in the management of hemophilia. Whereas before patients had to endure a life-threatening and crippling scourge, the increased availability of plasma concentrates of coagulation factors made from plasma pooled from thousand of donors and the widespread adoption of home care ('treatment at the doorstep') transformed hemophiliacs into individuals able to take full advantage of their talents and opportunities. Hemophilia care became one of the most gratifying examples of successful secondary prevention of a chronic disease. It was known that coagulation factor concentrates were contaminated with the virus causing non-A, non-B hepatitis (later identified as the hepatitis C virus). At that time, however, the peculiar epidemiology of hepatitis C, with the long time interval between infection and the occurrence of severe consequences such as cirrhosis and hepatocellular carcinoma, was not well established and chronic hepatitis appeared mild, with little negative effects on the well-being and life style of hemophiliacs.

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This optimistic perception of the infectious adverse effects of hemophilia treatment changed dramatically with the emergence of AIDS. The scientific community reacted rapidly to the new scourge, not only through progress in DNA technologies, that led at the beginning of the 1990s to the availability for treatment of recombinant factor (F)VIII and IX and to the first studies on gene transfer, but also with the development of methods meant to inactivate any blood-borne virus contained in concentrates. These developments, which took place in the years between 1983 and 1987, halted first the AIDS epidemic and subsequently that of non-A, non-B hepatitis. This pace of progress towards safer concentrates may look quite fast if one considers the hurdles that are often encountered in the development of innovative treatments. Yet, the communities of hemophilia treaters and of manufacturers of coagulation factors have been blamed for not having taken action fast enough. Many colleagues of mine have been involved in dramatic judicial events that devastated their professional and personal lives.

I offer this Historical Sketch on the critical years marked by the onset of the AIDS epidemics and the development of virus inactivation (virucidal) methods for large plasma pool factor concentrates. I first discuss the issues related to hepatitis and then those of human immunodeficiency virus (HIV) infection, not only for reasons of chronology but also because an understanding of the progress of our knowledge of hepatitis in persons with hemophilia, as well as the limited efficacy of the early measures taken to tackle this problem, is essential to understand how the problems of HIV infection and AIDS were subsequently tackled.

Hepatitis

Emergence of the hepatitis problem

Through the 1970s, it was recognized that the use of concentrates of coagulation factors made from plasma pooled from several thousands of blood donations was often associated with hepatitis [1]. However, the first large study of liver function tests was published in 1975 [2]. Our survey of 91 multitransfused Italian hemophiliacs found that 45% of them had elevated serum transaminases. Although non-A, non-B hepatitis

virus(es) was suspected to be responsible for transaminase abnormalities, a definite distinction between transfusion-associated hepatitis and 'transaminitis', i.e. enzyme elevations due to non-viral factors (such as, for example, drugs used to control pain, hypersensitivity reactions to allogeneic proteins present in clotting factor concentrates and tissue damage following intramuscular bleeding) [3] could not be made at that time. Our findings were subsequently confirmed and extended by a joint American/English study, that demonstrated that transaminase abnormalities persisted, supporting the views that they were a hallmark of chronic viral hepatitis [4].

Unequivocal evidence of the existence of structural liver disease in patients with hemophilia and elevated transaminases first came in 1977. Presenting the results of their liver biopsy investigations of six patients with hemophilia A and elevated serum transaminases, Lesesne *et al.* [5] diagnosed mild forms of chronic active hepatitis in three patients and chronic persistent hepatitis in the remaining three, but no case of cirrhosis. A prospective biopsy study [6] was undertaken by me with the hepatologists Colombo and Rizzetto in 10 hemophiliacs with non-A, non-B chronic hepatitis followed up for more than 6 years. The study, published in 1982, demonstrated no case of progression towards cirrhosis or hepatocellular carcinoma.

The relatively benign picture of non-A, non-B hepatitis initially emerging from these studies was questioned by three subsequent studies published in 1985 and 1986. A large retrospective survey of liver biopsies collected by Aledort *et al.* from hemophilia centers worldwide provided histological evidence of cirrhosis in 15% of cases [7]. In an 8-year prospective study conducted in Sheffield, histological signs of cirrhosis were found in nine of 79 hemophiliacs (12%) with chronic non-A, non-B infection [8]. In a retrospective biopsy study published in 1986 [9] Schimpf *et al.* found that cirrhosis developed in 13% of multitransfused German hemophiliacs during a follow-up of 13 years.

Hence, it was only in the mid 1970s that it became clear that hepatitis was frequent in hemophiliacs and it was only in the mid 1980s that it was shown to be progressive and severe in approximately one-sixth of patients. Beforehand, the view at the time held by me and, as far as I am aware, the great majority of hemophilia treaters was that the problem of hepatitis was a tolerable one, because the benefits of concentrates seemed to outweigh risks. In the 1960s and 1970s severe liver disease was not a prominent cause of death in hemophilia [10]. The most significant cause of death remained bleeding, particularly intracranial bleeding [10]. Hence, for severe hemophiliacs, there was no alternative but to continue the life-saving concentrate treatment despite the risks of hepatitis.

DDAVP and cryoprecipitate as alternative to concentrates

It was in treating mild hemophiliacs (who bleed only after spontaneous or surgical trauma and have little risk of death and disability from bleeding) that the risk of chronic hepatitis was less acceptable and it was with a view to find alternative treatments for the mild hemophiliacs that I undertook a clinical

trial of desmopressin (DDAVP), a synthetic drug derived from the antidiuretic hormone vasopressin which carries no risk of transmission of hepatitis and other blood-borne infections [11]. In April 1977 my colleagues and I demonstrated that DDAVP caused an increase in FVIII and was therefore an effective form of treatment for dental or general surgery in these infrequently treated patients [11]. The advantages of DDAVP in decreasing the risk of blood-borne infections in mild hemophilia were immediately appreciated in my country. The early use of DDAVP eventually led to a significantly lower rate of infection with HIV in Italian patients with mild hemophilia A compared with those with mild hemophilia B (who are unresponsive to DDAVP and can only use blood products) and with US patients with mild hemophilia A (who started using DDAVP much later than in Italy, in the mid 1980s) [12]. Plainly, the scientific community outside Italy needed some time to seek confirmation of the value of the treatment, so that DDAVP was not used on a large scale before the mid 1980s.

The choice to use single-donor cryoprecipitate, as opposed to large pool concentrates, was really only pertinent when considering mild hemophiliacs who are infrequently treated. In severe hemophiliacs, who receive frequent transfusions, perhaps three or more times a month, even small-pool or single-donor cryoprecipitate eventually results in exposure to the risk of contracting hepatitis, because of the ultimate patient's contact with plasma from a huge number of donors. Single-donor or small-pool cryoprecipitate or even fresh-frozen plasma can only delay the development of hepatitis, not certainly reduce or abolish it [13].

Heat treatment and other virucidal methods

The first attempt to treat large-pool concentrates with methods meant to decrease or abolish the risk of transmission of the hepatitis viruses was made by a German manufacturer that as early as in 1982 reported that no hepatitis ensued in a small group of normal volunteers infused with a prothrombin complex concentrate in which virus inactivation was attempted by adding the chemical β -propiolactone and ultraviolet light [14]. This report raised a number of ethical questions, not only for the fact that volunteers had been recruited among corporate staff but also because β -propiolactone was viewed as a potentially carcinogenic compound.

Subsequently another German manufacturer produced a FVIII concentrate which was pasteurized to inactivate the hepatitis viruses. The first information appeared in 1980 in a house journal of the company. I, like other clinicians, was unimpressed with the claim, because clinical evidence was meager and the design of the study retrospective and poor. In addition, the pasteurized concentrate was not available commercially in most European countries, and indeed there was insufficient concentrate to meet Germany's demands. Even German authorities resisted its use, because the concentrate was two or three times more expensive than unheated products and the evidence that there was any advantage in it was sparse. Indeed, it was not until 1987 and 1989 that studies by Schimpf

et al. scientifically established that the product did not transmit hepatitis and HIV [15,16].

In the early 1980s an American manufacturer developed a FVIII concentrate heated in the lyophilized state at 60 °C for 72 h. Experiments conducted in susceptible chimpanzees demonstrated that non-A, non-B hepatitis was not transmitted, but that hepatitis B was transmitted. The study reporting these data was published in full only in 1985 [17], even though many of us knew about the results beforehand.

It was only at the beginning of the 1980s that attempts to validate clinically methods capable of inactivating or removing the hepatitis viruses and applicable to coagulation factor concentrates started on a scientific basis. To provide recommendations for the design of meaningful clinical studies, the International Committee on Thrombosis and Haemostasis (ICTH) at a conference held in Miami, concluded that only highly susceptible patients should be studied, i.e. previously untreated patients (PUP). This recommendation was based on evidence indicating that previously untreated hemophiliacs developed hepatitis at a rate close to 100% upon their first exposure to large-pool concentrates, also those made from unpaid donors [18,19].

Adopting the ICTH recommendations, prospective studies were initiated using heat-treated products. In June 1983, during the Stockholm Congress of the World Federation of Hemophilia, the manufacturer of coagulation factor concentrate previously evaluated only in chimpanzees [17] summoned a group of hemophilia treaters and proposed a study to evaluate whether or not the FVIII concentrate, heated in the lyophilized state at 60 °C for 72 h, transmitted hepatitis. I enrolled in the study a relatively large number of patients in Italy as soon as I was back from Stockholm. From the follow-up of the first few enrolled patients it was clear that the virucidal procedure was ineffective, because practically all patients developed non-A, non-B hepatitis after the first infusion. The study continued to enroll more patients, so that it was only in July 1985 that with Colombo we published the data of the first study carried out under the rules of the International Committee [20]. The results showed that the concentrate transmitted non-A, non-B hepatitis to as many as 11 of the 13 patients. During the next few months, other studies evaluated concentrates heated in the lyophilized state at temperatures between 60 °C and 68 °C for different period of times (between 24 and 72 h) and similarly high rates of hepatitis virus transmission were found (references in a review) [21].

These ineffective early methods were abandoned and more efficacious methods were looked for and developed. In the next 2–3 years (1986–1988) there were several publications indicating that second-generation virucidal methods (pasteurization, dry-heating at higher temperatures such as 80 °C or more, vapor-heating, solvent-detergent) were better than the early heating methods and that they substantially reduced or abolished the occurrence of hepatitis after administration of large-pool concentrates [21]. Hence, the epidemics of hepatitis C were effectively halted in hemophiliacs in 1987–1988. Success was related not only to the continuous improvement of methods used by concentrate manufacturers to inactivate or remove

viruses (see above), but also to improvements in donor selection and screening. In this context, a major role was played by the isolation in 1989 of the virus causing non-A, non-B hepatitis (called the hepatitis C virus), the development of a serological test to screen donors and its adoption in 1991 to screen plasma used for fractionation.

HIV infection and AIDS

Everybody was in doubt in the early 1980s about the cause of AIDS, how it spread, how many persons with hemophilia actually got it and about the outcome of the disease. In 1982, worldwide, there was only a report of two hemophiliacs who had developed AIDS [22]. In 1983 there were no more than 10–15 full-blown cases, and many of us had not seen a case until 1984. It also must be borne in mind that although by 1983 many of us had the view of a possibility that the cause of AIDS might be a virus, there were alternative theories. The idea of the immune system being compromised by the constant use of concentrates was well supported [23,24].

It was around the end of 1983 to beginning of 1984 that lymphotropic retroviruses were isolated from patients with AIDS by Montagnier [25] and Gallo [26]. It must be emphasized, though, that there was at that time no demonstration that these viruses were the cause of AIDS rather than casual associations. Having heard in September 1984 that mouse retroviruses [27] and the human retrovirus putative agent of AIDS isolated by Montagnier [lymphadenopathy-associated virus (LAV)] could be inactivated by heating (but the latter data were fully published only in January 1985) [28], I met Montagnier in Paris in October 1984 and we chose to evaluate, with a preliminary serological test developed by him, some of the serum samples that Colombo and I had previously collected from hemophiliacs enrolled in the study on the effect on hepatitis of heat treatment at 60 °C for 72 h [20]. In a February 1985 issue of the *Lancet*, we reported in a letter to the Editor an absence of antibodies to LAV in patients treated exclusively with a concentrate heated at 60 °C for 72 h [29]. This was the first demonstration that dry-heating could inactivate the AIDS virus contaminating clotting factor concentrates used for hemophilia treatment.

Although there were earlier proponents of the theory that heat-treating the concentrates would be effective against AIDS as its causative agent might be a virus, the evidence was not available before the February 1985 report. It must be pointed out that the study carried out by Colombo *et al.* [20] to avoid the transmission of hepatitis had led to unsatisfactory results with regard to dry heating. This knowledge, albeit only published in July 1985, was already made available to the scientific community in 1983, because as I said before it was evident from the follow-up of the first few patients enrolled in our study that a large number of them had developed hepatitis. Such information was verbally communicated by me to a large number of hemophilia treaters who met in Barcelona on the occasion of the Congress of the European Society of Haematology in September 1983. It was also provided by an anonymous leading

Table 1 Chronology of the main events in the hepatitis and AIDS epidemics in persons with hemophilia

Year	Hepatitis Event	Year	AIDS Event
1970–1972	Early reports of hepatitis in persons with hemophilia treated with large-pool plasma concentrates [1]	1982, July	<i>Pneumocystis carinii</i> pneumonia in 3 hemophiliacs [22]
1975	First report of high prevalence of 'transaminitis' in persons with hemophilia [2]	1982, December	First transfusion-related case in an infant
1977	First report of liver biopsy in hemophiliacs [4]	1983, May	Isolation of lymphotropic retrovirus from a patient at risk of AIDS [23]
1977	Discovery of desmopressin (DDAVP) [11]	1984, May	Report of detection of HTLV-III in patients with AIDS or at risk of AIDS [25]
1980–1982	Development of a dry-heated concentrate and first experiments in chimpanzees [17]	1985, January	Evidence that heating inactivates the putative AIDS virus [27]
1983	Knowledge of transmission of non-A, non-B hepatitis by a heated factor VIII concentrates (Barcelona meeting)	1985, February	No transmission of AIDS virus by a factor VIII concentrate heated at 60 °C for 72 h [29]
1985–1986	Publication of the corresponding papers [20,21]		
1987	No transmission of hepatitis by a pasteurized factor VIII concentrate [15]		

article published in the last December 1984 issue of the *Lancet* that, referring to heat-treated concentrates, wrote 'their clinical efficacy vis-à-vis AIDS and seroconversions remains to be studied in previously unexposed patients' [30]. In 1983 and early 1984 there was little reason to believe that a heating procedure that was incapable of inactivating the hepatitis viruses, in particular the virus causing non-A, non-B hepatitis [20], should be more efficacious against the putative viral agent causing AIDS. Moreover, there were concerns about the potential risk of denaturation induced by heating on a labile protein such as FVIII and about the possibility of increased production of antibodies (inhibitors) to FVIII [31], with the view that drastic changes in the manufacturing process, such as those induced by heating, could affect the shape of the molecule and result in denaturation and neoantigenicity [31].

Although some extreme views were held that hemophiliacs should not receive concentrates, there was in my view little alternative during that period but to continue treating. I certainly told hemophiliacs under my care of the risk of AIDS from the early stages, but if one balances the risks that were known at that time against the substantial, well-perceived benefits of concentrate treatment, it is not surprising that very few of them elected to discontinue the use of factor concentrates.

The fallacy of retrospective knowledge

Table 1 summarizes the chronology of the development of knowledge about hepatitis and AIDS in hemophiliacs. To sum up, even though the problem of hepatitis was known since the 1970s, there was no reason to believe that this adverse effect of hemophilia care was heralding the much more ominous AIDS. On the whole, everybody was muddled in the period between the early 1980s, when the cases of the first two persons with hemophilia and AIDS were reported [22], and February 1985, when Montagnier and I showed for the first time that hemophiliacs treated with heated concentrates did not become infected with the retrovirus that in the same year was convincingly shown to be the cause of AIDS [29]. The failure of early

virucidal methods based on heating to inactivate the hepatitis virus was misleading, because it did convince many of us that the method had little virucidal activity, not only against the non-A, non-B virus but also, by implication, against other blood-borne agents.

The view and arguments presented here are certainly not exciting for the media, which prefer stories about preventable disasters with their related blame on the medical community, nor perhaps for governmental health authorities that tend to avoid any type of criticism that may be turned against them. Perhaps they will not even be popular among patients and their families, who do not forgive our failure to predict (and prevent) the devastating tragedy that befell them. With this Historical Sketch my intent was merely to recollect my hopefully objective but yet unconsciously biased memoirs on events that have dramatically affected so many lives.

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